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(71)(72) Applicant and Inventor: RAJADHYA J. [US/US]; 27436 Esquina, Mission Vi (US).				
(74) Agent: HUBBARD, Grant, L.; 300 South Suite 805, Anaheim, CA 92805 (US).	h Harbor B	lvd.		
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(54) Title: TDANSDEDMAI AND SYSTEM	AC DRED	4 D 4	TION AND METHOD	

(54) Title: TRANSDERMAL AND SYSTEMIC PREPARATION AND METHOD

(57) Abstract

Physiologically active azepines, pyrrolidines and piperidines for enhancing penetration of physiologically active agents.

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TRANSDERMAL AND SYSTEMIC PREPARATION AND METHOD Background of the Invention

Many physiologically active agents are best applied topically to obtain desirable results. Topical application, in the form of creams, lotions, gel, solutions, et., largely avoids side effects of the agents and permits high level concentrations of the agents.

Some therapeutive drugs may also be administered for systemic use through the skin or other body membranes 10 including intranasal and intravaginal application of humans and other animals, utilizing a transdermal device or formulated in a suppository or aerosol spray. For some years, pharmaceutical researchers have sought an affective means of introducing drugs into the bloodstream by 15 applying them to the unbroken skin. Among other advantages, such administration can provide a comfortable, convenient and safe way of giving many drugs now taken orally or infused into veins or injected intramuscularly.

Using skin as the portal for drug entry offers 20 unique potential, because of transdermal delivery permits close control over drug absorption. For example, it avoids factors that can cause unpredictable absorption from gastrointestinal tract, including: changes in acidity, motility, and food content. It also avoids initial metabolism of the drug by the liver, known as the first pass effect. Thus, controlled drug entry through skin can achieve a high degree of control over blood concentrations of drug.

Close control over drug concentration in blood 30 can translate readily into safer and more comfortable When a drug's adverse effects occur at higher treatment. concentrations than its beneficial ones, rate control can maintain the concentration that evoke only principally the drug's desired actions. This ability to 35 lessen undesired drug actions can greatly reduce the toxicity hazards that now restrict or prevent the use of many valuable agents.

many valuable agents.

Transdermal delivery particularly benefits patients with chronic disease. Many such patients have difficulty following regimens requiring several doses daily of medications that repeatedly cause unpleasant symptoms. They find the same drugs much more acceptable when administered in transdermal systems that require application infrequently - in some cases, only once or twice weekly - and reduce adverse effects.

Transdermal delivery is feasible for 10 effective in amounts that can pass though the skin area and that are substantially free of localized irritating or allergic effects. While these limitations may exclude some agents, many others remain eligible for transdermal 15 delivery. Moreover, their numbers will expand pharmaceutical agents of greater potency are developed. Particularly suitable for transdermal delivery are potent drugs with only a narrow spread between their toxic and safe blood concentrations, those having gastrointestinal 20 absorption problems, those susceptible to a higher first pass liver metabolism or those requiring frequent dosing in oral or injectable form.

Transdermal therapy permits much wider use of natural substances such as hormones. Often the survival times of these substances in the body are so short that they would have to be taken many times daily in ordinary dosage forms. Continuous transdermal delivery provides a practical way of giving them, and one that can mimic the body's own patterns of secretion.

At present, controlled transdermal therapy appears feasible for many drugs used for a wide variety of ailments including, but not limited to, circulatory problems, hormone dificiency, respiratory ailments, and pain relief.

Percutaneous administration can have the advantage of permitting continuous administration of drug

to the circulation over prolonged period of time to obtain a uniform delivery rate and blood level of drug. Commencement and termination of drug therapy are initiated by the application and removal of the dosing devices from 5 the skin. Uncertainties of administration through the gastrointestinal tract and the inconvenience administration by injection are eliminated. Since a high concentration of drug never enters the body, problems of pulse entry are overcome and metabolic half-life is not a 10 factor of controlling importance.

The greatest problems in applying physiologically active agents topically or transdermally is that the skin is an effective barrier to penetration. The epidermis of the skin has an exterior layer of dead 15 cells called the stratum corneum which compacted and oily and which provides an effective barrier against gaseous, solid or liquid chemical agents, whether used alone or in water or in oil solutions. physiologically active agent penetrates the stratus 20 corneum, it can readily pass through the basal layer of the epidermis and into the dermis.

Although the effectiveness of corneum as a barrier provides great protection, it also frustrates efforts to apply beneficial agents directly to 25 local areas of the body. The inability of physiologically active agents to penetrate the stratum corneum prevents their effective use of treating such conditions inflammation, acne, psoriasis, herpes simplex, infections caused by fungi, viruses 30 microorganisms, or other disorders or conditions of the skin or mucous membranes, or of conditions beneath the exterior surface of the skin or mucous membranes. stratum corneum also prevents the skin from absorbing and retaining cosmetic-type materials such as sunscreens, 35 perfumes, mosquito repellants and the like.

Physiologically active agents may be applied to

the locally affected parts of the body in the form of a solution, cream, lotion or gel utilizing the vehicle system described herein. These agents may also delivered for systemic use utilizing the vehicle system in 5 a transdermal patch. Vehicles such as USP cold cream, ethanol and various ointments, oils, solvents emulsions have been used heretofore to apply physiologically active ingredients locally. Most such vehicles are not effective to carry significant amounts of 10 physiologically active agents into and through the skin. One such vehicle is dimethyl sulfoxide, which is described in U.S. Patent No. 3,551,554.

My previous inventions disclosed in U.S. Patent Nos. 3,989,816; 3,991,203; 4,122,170; 4,316,893; 15 4,415,563; 4,423,040; 4,424,210; 4,444,762 describe a method for enhancing the topical administration of physiologically active agents by combining such an agent with an effective amount of a penetration enhancer and applying the combination topically to humans or animals, 20 in the form of solution, cream, gels, lotions etc. This prior art discloses N-alkyl substituted cyclic lactams as penetration enhancers.

My related U.S. Patent 4,405,616, describes a method for administering systemically active agents 25 through the skin or other body membranes of humans and animals, utilizing a transdermal device or formulation containing an effective amount of a suitable membrane penetration enhancer selected from the disclosed N-alkyl substituted cyclic lactams.

Penetration enhancers for enhancing systemic administration of therapeutic agents transdermally disclosed in the art include dodecyl pyrrolidone, dimethyl lauramide and dimethyl sulfoxide. The prior art states that these agents may be used prior to or concurrently 35 with administration of the active agent, e.g. see U.S. Patent Nos. 4,031,894; 3,996,934 and 3,921,636.

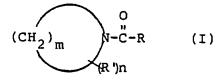
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SUMMARY OF THE INVENTION

The invention relates to compositions for carrying physiologically active agents through body membranes such as skin and for retaining these agents in body tissues and further relates to a method administering systemically active agents through the skin or other body membranes of humans and animals, utilizing a transdermal device or formulation, containing effective, non-toxic amount of a membrane penetration enhancer having the structural formula I:



where, R is an alkyl group with from 1 to 19 carbon
atoms;

wherein m = 4, 5 and 6 n = 0 - 4

and R' = H or COOH

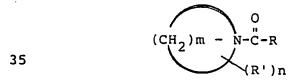
In one preferred embodiment, R is 6 to 19 In another preferred embodiment of

25 (CH₂)m - N-C-R

where m is 4 to 6, R is 1 - 19, R' is H and n is 1.

The preferred compound is 1-dodecanoylhexahydro-lH-azepine.

In another preferred embodiment,



m is 4 to 6, R is 1 to 19, R' is COOH and n is 1. The preferred compounds are in which m is 4 and 5, R' is 2-COOH, and R is 11, for example,

1-dodecanoyl-2-carboxypyrrolidine

5 and

1-dodecanoy1-2-carboxypiperidine.

It has been found that the physiologically active agents are carried through body membranes by the claimed penetration enhancers and are retained in the body 10 tissue when applied topically in form of a cream, gel or lotion or absorbed systemically when applied in the form of a transdermal device or formulation, for example, as a rectal or vaginal suppository, as a nasal spray or when incorporated in a vaginal sponge.

15 DETAILED DESCRIPTION OF THE INVENTION

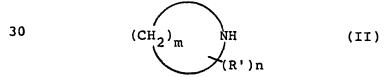
Typical examples of compounds included in the foregoing formula I of this invention are the following:

- 1) 1-butyrylpyrrolidine
- 2) 1-pentanoylpyrrolidine
- 3) 1-hexanoylpyrrolidine
 - 4) l-octanoylpyrrolidine
 - 5) 1-nonanoylpyrrolidine
 - 6) l-decanoylpyrrolidine
 - 7) l-dodecanoylpyrrolidine
- 8) l-tetradecanoylpyrrolidine
 - 9) 1-hexadecanoylpyrrolidine
 - 10) 1-pentanoylpiperidine
 - 11) 1-hexanoylpiperidine
 - 12) 1-heptanoylpiperidine
- 30 13) 1-octanoylpiperidine
 - 14) 1-nonanoylpiperidine
 - 15) 1-decanoylpiperidine
 - 16) 1-dodecanoylpiperidine
 - 17) l-tetradecanoylpiperidine
- 35 18) 1-hexadecanoylpiperidine
 - 19) 1-butyrylhexahydro-lH-azepine

	20	l-pentanoylhexahydro-lH-azepine
	21	l-hexanoylhexahydro-lH-azepine
	22)	l-heptanoylhexahydro-lH-azepine
	23)	l-octanoylhexahydro-lH-azepine
5	24)	l-nonanoylhexahydro-lH-azepine
	25)	l-decanoylhexahydro-lH-azepine
	26)	•
	27)	
	28)	_
10	29)	_
	30)	
	31)	
	32)	l-decanoy1-2-carboxypyrrolidine
	33)	1-dodecanoy1-2-carboxypyrrolidine
15	34)	l-tetradecanoyl-2-carboxypyrrolidine
	35)	1-hexadecanoy1-2-carboxypyrrolidine
	36)	l-hexanoyl-2-carboxypiperidine
	37)	l-octanoyl-2-carboxypiperidine
	38)	l-decanoyl-2-carboxypiperidine
20	39)	l-dodecanoyl-2-carboxypiperidine
	40)	1-tetradecanoy1-2-carboxypiperidine
	41)	l-hexadecanoyl-2-carboxypiperidine
	42)	l-hexanoyl-3-carboxypiperidine
	43)	1-octanoy1-3-carboxypiperidine
25	44)	l-decanoyl-3-carboxypiperidine
	45)	l-dodecanoyl-3-carboxypiperidine
	46)	1-tetradecanoy1-3-carboxypiperidine
	47)	1-hexadecanoy1-3-carboxypiperidine
	48)	l-hexanoyl-4-carboxypiperidine
30	49)	l-octanoyl-4-carboxypiperidine
	50)	l-decanoyl-4-carboxypiperidine
	51)	l-dodecanoyl-4-carboxypiperidine
	52)	l-tetradecanoyl-4-carboxypiperidine
	53)	1-hexadecanoy1-4-carboxypiperidine
35		

The following compounds, encompassed by general formula I of this invention are known in the literature. Compounds, 14 and 23-25 were evaluated for pungency [Rice et. a., J. Amer. Chem. Soc. 76,3730 (1954)]. 5 2-28 were evaluated for insect repellent [McGovern et. al., J. Ga. Entomol. Soc. 14,166 (1979); Alexander et al., J. Econ. Entomol., 56, 58 (1963); J. Chem. Eng. Data, 7,263 (1962); Davydova et al., Chem. Abstr., vol. 71, 122670j (1969); compounds 15 and 25 for 10 antimicrobial activity [Novak et al., J. Amer. Oil Chem. Soc. 46,249 (1969)]; compounds 10-12 and 18 for mimicking pepper constituents [Staudinger et. al., Ber., 56B, 699 (1923)]; compounds 29-32, 34 and 35, are known [Kikuchi et. al., Biochim. Biophys. Acta, 744, 180 (1983)] as the 15 substrates for the enzyme Proline Acylase. Compound 33 is known in the literature to possess plant growth regulating activity [Kider et. al., Agric. Biol. Chem., (1976)]; and compound 33 as a surface active agents for thermal denaturation of DNA [Tsuji, J. Amer. Oil Chem. 20 So., 54,585 (1977)]. Compounds 44-53 to my knowledge are The use of the compounds of the present invention as penetration enhancers is, however, novel predictable from the prior art.

The compounds covered by the general formula I may be prepared by any of the processes known for the preparation of acid amides. For example, (1) a carboxylic acid, R-COOH, is made to react directly with an amine of the formula II,



(wherein m, n, R and R' are as defined above) in the absence or presence of such dehydrating agents as a disubstituted carbodiimide compound, carbonyl diimidazole,

p-toluenesulphonic acid, p-toluenesulphonyl chloride or acetic anhydride [Starkov et. al., Chem. Abstr., 72,31583 (1970)], in an aqueous or organic solvent, (2) a carboxylic acid halide, R-CO-X (where X is Cl or Br), prepared from a carboxylic acid, R-COOH, and the resulting acid halide is treated with at least an equimolar amount of the amine II, in the presence of a basic condensing agent [Alexander et. al., J. Econ. Entomol., 56,58 (1963); Kukuchi et. al., Biochim. Biophys. Acta 744,180 (1963)], 10 (3) a lower alkyl ester of a carboxylic acid, R-COOR1 (where R1 is lower alkyl group with 1-3 carbons) is made to react directly with the amine, II, in the presence or absence of a solvent and condensing agent, (4) a mixed acid anhydride of a carboxylic acid of the formula,

15

(wherein R is as defined above and R_2 is an alkyl or 20 haloalkyl radical having 1-20 carbon atoms) is made to react with the amine, II, in the presence of a basic condensing catalyst, (5) amine of formula II is treated with a carboxylic acid in the presence of trimethylamineborane in an aromatic hydrocarbon solvent, such as xylene 25 [Trapani et. al., Synthesis, 1013 (1983)] transamidation of formylpiperidine and formylhexamethyleneimine with a carboxylic acid over 220 C [Naumov et. al., Chem. Abstr., 76, 85678u (1972)].

The compounds of the present invention may be 30 used as penetration enhancers in the same manner as described in my U.S. Patents 3,989,816; 3,991,203; 4,415,563; 4,122,170; 4,316,893; 4,423,040; 4,424,210 and 4,444,762, which are hereby incorporated by reference.

The compounds of the present inventions are 35 useful as penetration enhancers for a wide range of physiologically active agents and the compositions

disclosed herein are useful for topical and transdermal effect of these agents. Typically therapeutic agents which be delivered systemically active may which therapeautic agents are transdermally are 5 sufficiently potent such that they can be delivered through the skin or other membranes to the bloodstream in sufficient quantities to produce the desired therapeutic effect. In general this includes agents in all of the major therapeutic areas including, but not limited to, 10 anti-infectives, such as antibiotics and antiviral agents, anthelmintics, antiarthritics, analgesics, anorexics, antiasthma agents, anticovulsants, antidepressants, antidiabetic agents, antimigraine preparations, antimotion sickness, antinauseants, antineoplastics, antiparkinsonism antipruritics, antipsychotics, antipyretics, 15 drugs, antispasmodics, including gastrointestinal and urinary; anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel beta-blockers, antiarrhythmics, blockers, 20 antihypertensives, diuretics, vasodilators including coronary, peripheral and cerebral; central nervous system stimulants, cough and cold preparations, hormones, hypnotics, diagnostics, decongestants, immunosuppressives, muscle relaxants, parasympatholytics,

25 parasympathomiemetcs, sedatives and tranquilizers. For topical applications the agents include antibiotics, fungistatic and fungicidal corticosteroids, agents, antiemetics, antpruritic agents, vasodilators, bronchodilators, expectorants, analgesics, 30 sunscreen compounds, collagen softening agents and other similar compounds. Cosmetic agents, hair and skin dyes, synthetic and hormones, perfumes, repellents, diagnostic agents and other such compounds may also be advantageously formulated with these penetration 35 enhancers.

Some of these penetration enhancers can also be

used by themselves as moisturizers in cosmetic formulations. Moreover, these penetration enhancers are useful in agriculture in the application of fertilizers, hormones, growth factors including micronutrients, 5 insecticides, molluscicides, arachicides, nematocides, rodenticides, herbicides, and other pesticides to plants, animals and pests. These penetration enhancers are also useful for penetration of micronutrients in seeds for enhanced plant growth.

- Of course, the appropriate dosage levels of all 10 the physiologically active agents, without conjoint use of the penetration enhancing compounds of formula I, known to those of ordinary skill in the art. conventional dosage levels correspond to the upper range dosage levels for compositions including physiologically active agent and a compound of formula I as a penetration enhancer. However, because the delivery of the active agent is enhanced by compounds of the present invention, dosage levels significantly lower than 20 conventional dosage levels may be used with success. Systemically active agents are used in amounts calculated to achieve and maintain therapeutic blood levels in a human or other animal over the period of time desired. (The term "animal" as used here encompasses humans as well 25 as other animals, including particularly pets and other domestic animals.) These amounts vary with the potency of each systemically active substance, the amount required for the desired therapeutic or other effect, the rate of elimination or breakdown of the substance by the body once has entered the bloodstream and the
- it has entered the bloodstream and the amount of penetration enhancer in the formulation. In accordance with conventional prudent formulating practices, a dosage near the lower end of the useful range of a particular agent is usually employed initially and the dosage increased or decreased as indicated from the observed response, as in the routine procedure of the physician.

The present invention contemplates compositions of compounds of formula I, together with physiologically active agents from 0.05% to 100% of conventional dosage The amount of carboxylic acid amide which may be 5 used in the present invention is an effective, non-toxic amount for enhancing percutaneous abosrption. Generally, for topical use the amount ranges between 0.01 to about 10 and preferably about 0.1 to 5 percent by weight of the composition. For transdermal enhancement of systemic 10 agents, the amount of penetration enhancer which may be used in the invention varies from about 1 to 100 percent although adequate enhancement of penetration is generally found to occur in the range of about 1 to 30 percent by weight of the formulation to be delivered. For 15 transdermal use, the penetration enhancers disclosed herein may be used in combination with the active agent or may be used separately as a pre-treatment of the skin or other body membranes through which the active agent is intended to be delivered.

20 Dosage forms for application to the skin or other membranes of humans and animals include creams, lotions, gels, ointments, suppositories, sprays, aerosols, buccal and sublingual tablets and any one of a variety of transdermal devices for use in the continuous 25 administration of systemically active drugs by absorption through the skin, oral mucosa or other membranes, see for example, one or more of U.S. Patent Nos. 3,598,122; 3,598,123; 3,731,683; 3,742,951; 3,814,097; 3,921,636; 3,972,995; 3,993,072; 3,993,073; 3,996,934; 4,031,894; 30 4,060,084; 4,069,307; 4,201,211; 4,230,105; 4,292,299 and U.S. Patent No. 4,077,407 and the foregoing 4,292,303. patents also disclose a variety of specific systemically active agents which may also be useful as in transdermal delivery, which disclosures are hereby incorporated herein 35 by this reference.

Typical inert carriers which may be included in

the foregoing dosage forms include conventional formulating materials, such as, for example, water, ethyanol, 2-propanol (isopropyl alcohol), 1,2-propanediol (propylene glycol), 1,3-butanediol, 1,2,3-propanetriol (glycerol), propanone (acetone), butanone (methyl ethyl ketone), freons, polyvinyl pyrrolidone, frangrances, gel producing materials such as "Carbopol", stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, sorbital, "polysorbates", "Tweens", methyl cellulose etc.

10. The examples which follow illustrate the penetration enhancers and the compositions of the present invention.

Example 1

Preparation of 1-hexanoylpyrrolidine

- Hexanoyl chloride (13.46 g, 0.1M) was added gradually to a cooled, stirred solution of pyrrolidine (7,25 g, 0.1M) in 200 ml of benzene and dry pyridine (7.91 g, 0.1M). Two hours after the addition water was added. The organic layer was washed successively with 5% aqueous
- hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. Distillation of the residue gave 13.52 g (80%) of a colorless oil, b.p. 98-100 / 7 mm.
- The following compounds were prepared analogously by substituting equimolar amount of the corresponding carboxylic acid chlorides:

l-octanoylpyrrolidine 83% 110-115 / 0.3 mm l-nonanoylpyrrolidine 76% 137 / 0.5 mm 30 l-tetradecanoylpyrrolidine 75% 177-180 / 0.3 mm l-hexadecanoylpyrrolidine 70% 200-205 / 1 mm

The following compounds are prepared analogously by substituting equimolar amounts of the corresponding carboxylic acid chlorides:

35 l-decanoylpyrrolidine
l-dodecanoylpyrrolidine

EXAMPLE 2

Preparation of 1-dodecanoylpiperidine

In a manner similar to that described in Example 1, dodecanoyl chloride (21.88 g, 0.1M) was treated with piperidine (8.52 g, 01M). Work up and distillation gave 16.55 g (62%) of the product, b.p. 185 / 2 mm.

The following compounds were prepared analogously by substituting equimolar amount of the corresponding carboxylic acid chlorides:

	l-pentanoylpiperidine	70 ቄ	122-125 /	' 10 mm
10	l-hexanoylpiperidine	71%	101-102 /	0.5 mm
	l-heptanoylpiperdine	70%	158-162 /	12m mm
	l-octanoylpiperidine	69%	101-102 /	0.3 mm
	l-nonanoylpiperidine	67%	105 /	0.1 mm
	l-decanoylpiperidine			
15	l-tetradecanoylpiperidine	63%	174 /	0.5 mm
	l-hexadecanoylpiperidine	57%	182 /	0.3 mm

Example 3

Preparation of 1-octanoylhexahydro-1H-azepine

In a manner similar to that described in Example 1, octanoyl chloride (16.26 g, 0.1M) was treated with hexahydro-1H-azepine (9.92 g, 0.1M). Work up and distillation of the residue gave 15.3 g (68%) of product, b.p. 122 / 0.8 mm.

The following compounds were prepared 25 analogously by substituting equimolar amount of the corresponding carboylic acid chlorides:

l-hexanoylhexahydro-lH-azepine 66% 112 / 0.8 mm l-nonanoylhexahydro-lH-azepine 84% 123-124 / 0.02 mm l-hexadecanoylhexahydro-lH-azepine 63% 205 / 0.5 mm

30 Example 4

Preparation of 1-dodecanoylhexahydro-lH-azepine
A mixture of dodecanoic acid (20.03 g, 0.1M),
acetic anhydride (13.27 g, 0.13M), hexahydro-lH-azepine
(12.9 g, 0.13M) was heated with distillation of formed

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-15-
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acetic acid. The residue on distillation gave 23.46 g (83.5%) of colorless product, b.p. 204-205 / 7 mm.

The following compounds were prepared analogously by substituting equimolar amount of the 5 corresponding carboxylic acids:

l-butyrylhexahydro-lH-azepine 63.2% 133-4 / 11 mm l-pentanoylhexahydro-lH-azepine 84% 141-2 / 7 mm l-decanoylhexahydro-lH-azepine 81% 181-3 / 6 mm

Example 5

Preparation of l-butyryl-2-carboxypyrrolidine (l-butyryl-L-proline)

11.4 m. (0.11M) of butyryl chloride and 20 ml of 7M NaOH (0.1M) were added in small portions into a chilled solution of L-proline (11.5 g, 0.1M) dissolved in 14.3 ml 15 7M NaOH (0.1M) according to the method of Kikuchi et. al., Biochim. Biophys. Acta 744,180 (1983). The reaction mixture was stirred vigorously during the addition and was always kept slightly alkaline. After the addition was over the reaction mixture was further stirred for an hour 20 at 0-5 C. The mixture was then extracted with one portion of ethyl acetate and the aqueous layer was acidified with HCl to pH 1.8. The precipitated product was washed with cold water and dried in vacuo. Recrystallization from acetone gave 14 g (82%) of the product.

25 The following compounds were similarly prepared by substituting equimolar amounts of the corresponding carboxylic acid chlorides:

l-hexanoyl-2-carboxypyrrolidine (l-hexanoyl-L-proline)
l-octanoyl-2-carboxypyrrolidine (l-octanoyl-L-proline)
l-decanoyl-2-carboxypyrrolidine (l-decanoyl-L-proline)
l-dodecanoyl-2-carboxypyrrolidine (l-dodecanoyl-L-proline)
l-tetradecanoyl-2-carboxypyrrolidine (l-tetradecanoyl-L-proline)
l-hexadecanoyl-2-carboxypyrrolidine (l-hexadecanoyl-L-proline)

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Example 6

The general procedure of Example 5 is repeated, except that the L-proline utilized therein is replaced, successively, with an equimolar amount 2-piperidinecarboxylic acid and butyryl chloride is 5 replaced, successively, with an equimolar amount of C6, C8, C10, C12, C14 and C16 carboxylic acid chlorides to produce, respectively

1-hexanoy1-2-carboxypiperidine

I-octanoyl-2-carboxypiperidine

10 l-decanoyl-2-carboxpiperidine

1-dodecanoy1-2-carboxypiperidine

1-tetradecanoy1-2-carboxypiperidine

1-hexadecanoy1-2-carboxypiperidine

Example 7

- The general procedure of Example 5 is repeated, except that L-proline utilized therein is replaced, successively, with an equimolar amount of 3-piperidinecarboxylic acid and butyryl chloride is replaced, successively, with an equimoloar amount of C6,
- 20 C8, C10, C12, C14 and C16 carboxylic acid chlorides to produce, respectively

1-hexanoy1-3-caroboxypiperidine

1-octanoy1-3-carboxypiperidine

l-decanoyl-3-carboxypiperidine

25 1-dodecanoyl-3-carboxypiperidine

1-tetradecanoyl-3-carboxypiperidine

1-hexadecanoy1-3-carboxypiperidine

Example 8

The general procedure of Example except that L-proline utilized 30 repeated, therein is replaced, successively, with an equimolar amount of 4-piperidinecarboxylic acid and butyryl chloride replaced, successively, with an equimolar amount of C6, C8, C10, C12, C14 and C16 carboxylic acid chlorides to 35 produce, respectively

Sodium citrate

Chemoderm #844 Fragrance

_	1	7	_
	_		

l-octanoyl-4-carboxypiperidine

l-decanoyl-4-carboxypiperidine

l-dodecanoyl-4-carboxypiperidine

5 l-tetradecanoyl-4-carboxypiperidine

l-hexadecanoyl-4-carboxypiperidine

Example 9

The following solution formulation is prepared

0.5

0.2

	,,,,,	
		Solution%
10	Griseofulvin	1
	l-dodecanoylhexahydro-lH-azepin	e 1
	Isopropyl myristate	5
	Fragrance	0.1
	Ethanol	92.9
15	This formulation is	effective in the treatment
	of fungus infections.	
	Example	10
	An aerosol form of th	e formulation of Example 10
	is prepared by preparing the fo	
20	Formulation	25%
	1	
	Freon	75%
	¹ Freon is 75/25 Freon 114/12	
	Example	11
25	The following cream for	ormulation is prepared:
		 ፟
	Clindamycin base	1.0
	Stearyl alcohol, U.S.P.	12.0
	Ethoxylated cholesterol	0.4
30	Synthetic spermaceti	7.5
	Sorbitan monooleate	1.0
	Polysorbate 80, U.S.P.	3.0
	l-dodecanoylhexahydro-lH-zaepine	≘ 0.5
	Sorbitol solution, U.S.P.	5.5
35	Sodium citrate	0.5

		-18-
	Purified water	68.4
	This formulation	is effective in the treatment
	of acne.	
	Exa	mple 12
5	The following	solution formulations are
	prepared:	·
		A (%) B (%)
	Clindamycin base	- 1.0
	Clindamycin phosphate acid	1.3 -
10	Sodium hydroxide	0.077
	lM Hydrochloric acid	- 2.27
	Disodium edetate. 2H2O	0.003 0.003
	Fragrances	0.5 0.5
	1-dodecanoylhexahydro-1H-az	epine 1.0 1.0
15	Purified water	20.0 17.73
	Isopropanol	77.12 77.497
	These solutions a	re effective for the treatment
	of acne in humans.	
		mple 13
20	The following solution	ution formulation is prepared:
		%
	Neomycin sulfate	0.5
	Lidocaine	0.5
	Hydrocortisone	0.25
25	l-dodecanoylhexahydro-lH-az	_
	Propylene glycol	98.25
		effective for the treatment of
	otitis in domestic animals.	
30		mple 14
30	The following sun	screen emulsion is prepared:
•	n_ominahoussis osid	₽ ·
	p-aminobenzoic acid	2.0
	Benzyl alcohol	0.5 epine 1.0
3.5	<pre>l-dodecanoylhexahydro-1H-az Polyethylene glycol 500-MS</pre>	10.0
. .	Isopropyl lanolate	3.0
	TRUDE TRUDE	3.0

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	-19-	
	Lantrol	1.0
	Acetylated lanolin	0.5
	Isopropyl myristate	5.0
	Light mineral oil	8.0
5	Cetyl alcohol	1.0
	Veegum	1.0
	Propylene glycol	3.0
	Purified water	64.0
	Example 15	
10	The following antineoplastic	solution is
	prepared:	
		8
	5-fluorouracil	5
	l-dodecanoylhexahydro-lH-azepine	0.1
15	Polyethylene glycol	5
	Purified water	89.9
	Example 16	
	The following insect repellant	atomizing spray
20	is prepared:	•
20		કૃ
	N,N-diethyltoluamide	0.5
	1-dodecanoylhexahydro-1H-azepine	0.5
	Ethanol	99
25	Example 17	
23	The following cream formulation	•
	containing about 0.001 to 1 percent, with percent fluocinolone acetonide:	preferably 0.1
	percent fluodinolone acetonide:	
		ક
30	Oil phase	15
	Fluocinolone acetonide	0.1
	l-dodecanoylhexahydro-lh-azepine	1
	cetyl alcohol	9.5
	Stearyl alcohol	1.5
35	Glyceryl monostearate	4
	<u> </u>	•

	Water pha	se						
	Propylene glycol							10
	Sodium dodecyl sulfate							0.1
	Deionized water q.s.							100
5		The	steroid	is	dissolved	in	the	vehicle

e and added to a stirred, cooling melt of the other ingredients. The preparation is particularly useful for the treatment of inflamed dermatoses by topical application to the affected skin area. The amount of frequency 10 application of this steroid. Penetration of the steroid in the inflamed tissue is enhanced and a therapeutic level is achieved more rapidly and sustained for longer duration than when the steroid is applied in conventional formulation.

15 Example 18

The following analgesic gel is prepared:

		욯
	Carbopol 934	1
	Indomethacin	1
20	Propylene glycol	10
	Ethanol	30
	Diisopropanolamine	. 1.1
	Diisopropyl adipate	2
	l-dodecylhexahydro-lH-azepine	2
25	Water	52.9

Example 19

The following cream formulation is prepared:

		용	
	Isosorbide dinitrate	10	
30	Glycerol monostearate	5.	5
	Polyoxyethylene stearate	4.	5
,	C8-C18 fatty acid esters of a glycerol		
	ethoxylated with about 7 moles of ethylene	oxide	8
	l-dodecanoylhexahydro-lH-azepine	2	
35	Sorbic acid	0.	165
	Ascorbyl palmitate	0.	055

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5		This	formulation	is	effective	in	the	treatment
	Water						69	.616
	Fragrance						0	.05
	Na EDTA						0	.014
	Citric ac	ıd					0	.1

nt of angina.

Example 20

The following skin moisturizing formulation is prepared:

10		do
	Pyrrolidonecarboxylic acid Na	1
	Glycerine	4
	Citric acid	0.03
	Sodium citrate	0.05
15	Allantoin	0.1
	Ethanol, 95%	9
	Oleth-15	1
	Linoleic acid	1
	l-dodecanoyl-L-proline	2
20	Sunscreen agent	0.1
	Water	81.72

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In addition to the above exemplified applications of the compositions and methods, the invention finds significant application in agricultural and others 5 biological fields. For example, the compositions and methods of the invention are useful in enhancing thepenetration of hybridization agents. Agents of this type are described in the literature. For example, the compositions of the present invention carrying pollen 10 suppressant agents such as the substituted dihydropyidazines described by Fang and Labovitz, U.S. Patent No. 4,561,881, in the concentration ranges shown in the examples above may be used to enhance the penetration and effectiveness of these agents. 15 Nitroarylalkylsulfone derivatives, as described by Fankhauser and Sturm, U.S. Patent No. 4,459,152, in a concentration of from about 0.01 to 1 percent may be applied as a growth stimulant to plants and seeds. Biochemical and biological agents for enhancing, 20 diminishing or terminating plant growth, for enhancing, diminishing or terminating fertility of plants, seeds, pollen and the like in solutions of the described compositions are highly advantageous in agricultural research and production. Other agricultural 25 applications include compositions comprising the enhancing of absorption of therapeutic and other livestock treating compositions.

Industrial Application

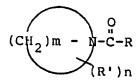
This invention finds application in the health care, pharmaceutical, animal husbandry and agricultural applications to enhance the penetration or absorption of biologically active agents.

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IN THE CLAIMS

WHAT IS CLAIMED IS:

1. Α composition useful for topically administering physiologically active agents through the 5 skin and mucous membranes of humans and animals in a transdermal device or formulation for systemic use or to the skin of humans and animals for localized use comprising an effective amount of a physiologically active agent and a non-toxic, effective penetrating amount of a 10 compound having the structural formula



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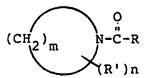
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where R is an alkyl group with 1 to 19 carbon atoms, m is 4, 5 or 6, R' is H and COOH and n is 0 to 4.

- 2. The composition of Claim 1 wherein the physiologically active agent is an antibacterial agent.
- 3. The composition of Claim 1 where in the antibacterial agent is an antibiotic.
 - 4. The composition of Claim 1 wherein the antibiotic is selected from the group consisting of lincomycin, clindamycin, erythromycin and pharmaceutically useful salts thereof.
 - 5. The composition of Claim 1 wherein the physiologically active agent is physiologically active steroid.
- 6. The composition of Claim 1 wherein the physiologically active agent is an antifungal agent.
 - 7. The composition of Claims 1 wherein the physiologically active agent is iododeoxyuridine.
 - 8. The composition of Claim 1 wherein the physiologically active agent is 5-fluorouracil.
- 9. The composition of Claim 1 wherein the physiologically active agent is an

anti-inflammatory/analgesic agent.

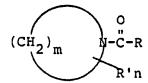
- 10. The composition of Claim 9 wherein the anti-inflammatory/analgesic active agent is selected from the group consisting of indomethacine, diclofenac, 5 ketoprofen, ibuprofen, fenamic acids and pharmaceutically acceptable salts thereof.
 - ll. The composition of Claim 1 wherein the physiologically active agent is bronchodilator or metaproterenol.
- 10 l2. The composition of Claim 1 wherein the physiologically active agent is an antipruritic agent.
 - 13. The composition of Claim 1 wherein the physiologically active agent is clonidine.
- 14. The composition of Claim 1 wherein the 15 physiologically active agent is a neuroleptic.
 - 15. The composition of Claim 1 wherein the physiologically active agent is a vasodilator.
- 16. The composition of Claim 15 wherein the vasodilator is selected from the group consisting of 20 nitroglycerine, isosorbide dinitrate and pentaerythritol tetranitrate.
- 17. A composition comprising an effective amount of a physiologically active agent and an effective penetrating amount of a compound having the structural 25 formula



- 30 where, R is an alkyl group with 4 to 19 carbon atoms, where, m is 4 to 6, R' is H and COOH and n is 0 to 4.
 - 18. A composition comprising an effective amount of a physiologically active agent and an effective, penetrating amount of 1-dodecanoylhexahydro-1H-azepine.
- 35 l9. A composition comprising an effective amount of a physiologically active agent and an effective,

penetrating amount of 1-dodecanoy1-2-carboxypyrrolidine.

- 20. A composition comprising an effective amount of a physiologically active agent and an effective, penetrating amount of 1-dodecanoy1-2-carboxypiperidine.
- 5 21. A method for topical administration of systemically active agents through the skin or mucosal membranes of humans and animals in a transdermal device or formulation, the improvement comprising the topical administration of an effective amount of a membrane penetration enhancer having the structural formula,



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25

30

where, is an alkyl group with 1 to 19 carbon atoms; R' is H, n is O, and m is 4 to 6.

- 22. The method of Claim 21 wherein R is 6 to 19.
- 23. The method of Claim 21 wherein m is 6.
- 24. The method of Claim 23 wherein R is 6 to 19.
- 25. The method of Claim 21 wherein the penetration enhancer is 1-dodecanoylhexahydro-lH-azepine.
 - 26. The method of Claim 21 wherein m is 4.
 - 27. The method of Claim 26 wherein R' is COOH.
 - 28. The method of Claim 26 wherein n is 1.
 - 29. The method of Claim 26 wherein R is 6 to 19.
- 30. The method of Claim 21 wherein the penetration enhancer is 1-dodecanoy1-2-carboxypyrrolidine.
- 31. The method of Claim 21 wherein the penetration enhancer is 1-dodecanoy1-2-carboxypiperidine.
- 32. The method of Claim 21 wherein the systemically active agent is a therapeutic agent.
- 33. The method of Claim 34 wherein the administration is concurrent.
- 34. A composition comprising a physiologically acceptable carrier and an amount of l-dodecanyl-2-carboxypyrrolidine effective to moisturize the skin to which such composition may be applied.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/02052

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 3 JPC TPC According to International Patent Classification (IPC) or to both National Classification and IPC 514/844, 847, 873, 946, 947, 969 604/896, 897 Ā61K 7/48 A61K 47/00 A61L 15/03 II. FIELDS SEARCHED Minimum Documentation Searched 4 Classification System Classification Symbols 514/844, 847, 873, 946, 947, 969 U.S. 604/896, 897 Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched 6 RAJADHYAKSHA, VITHAL J. III. DOCUMENTS CONSIDERED TO BE RELEVANT 14 Citation of Document, 16 with indication, where appropriate, of the relevant passages 17 Relevant to Claim No. 18 U.S,A, 3,711,606 (HERSCHLER) issued Α 1 to 34 16 January 1973, see entire document. A U.S,A, 3,742,951 (ZAFFARONI) issued 1 to 34 03 July 1973, see entire document. U.S,A, 3,989,815 (RAJADHYAKSHA) issued A 1 to 34 02 November 1976, see entire document. Α U.S,A, 3,989,816 (RAJADHYAKSHA) issued 1 to 34 02 November 1976, see entire document. Ą U.S,A, 3,991,203 (RAJADHYAKSHA) issued 1 to 34 09 November 1976, see entire document. A U.S,A, 3,996,934 (ZAFFARONI) issued 1 to 34 14 December 1976, see entire document. "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the * Special categories of cited documents: 13 "A" document defining the general state of the art which is not considered to be of particular relevance invention earlier document but published on or after the international filing date document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. document is combined with one or more other such docuother means document published prior to the international $5\log$ date but later than the priority data claimed "A" document member of the same patent family IV. CERTIFICATION Date of Mailing of this International Search Report 3 Date of the Actual Completion of the International Search . 08 DEC 1986 02 December 1986 International Searching Authority 1 Signature of Authorized Officer 29 Shep K. Rose ISA/US

International Application No.

	CONTINUED FROM THE SECOND SH	PCT/US86/0205
I. DOCUI	MENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND 97	Relevant to Claim No 18
ategory *	to with indication, where appropriate, or the restaurant	
A	U.S,A, 4,415,563 (RAJADHYAKSHA) issued 15 November 1983, see entire document.	1 to 34
A	U.S,A, 4,423,040 (RAJADHYAKSHA) issued 27 December 1983, see entire document.	1 to 34
A .	U.S,A, 4,424,210 (RAJADHYAKSHA) issued 03 January 1984, see entire document.	1 to 34
A.	U.S,A, 4,444,762 (RAJADHYAKSHA) issued 24 April 1984, see entire document.	1 to 34
A	U.S,A, 4,461,638 (RAJADHYAKSHA) issued 24 July 1984, see entire document.	
A	U.S,A, 4,525,199 (RAJADHYAKSHA) issued 25 June 1985, see entire document.	1 to 34
A	U.S,A, 4,557,934 (COOPER) issued 10 December 1985, see entire document.	1 to 34
A	U.S,A, 4,562,075 (RAJADHYAKSHA) issued 31 December 1985, see entire document.	1 to 34
A	U.S,A, 4,568,343 (LEEPER ET AL) issued 04 February 1986, see entire document.	1 to 34
A	U.S,A, 5,573,996 (KWIATEK ET AL) issued 04 March 1986, see entire document.	1 to 34
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